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Original Research

Cognitive functions in geriatric patients undergoing elective surgery

Cognitive functions in geriatric patients after surgery

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Abstract

Aim: The aim of this study is to examine the effect of general anesthesia on cognitive functions in geriatric patients and to make recommendations based on the results obtained.

The primary endpoint of the study is to investigate the effect of anesthesia on cognitive functions in geriatric patients with the Mini-Mental State test (MMST). Secondary endpoint; to compare our findings with other studies and evaluate the subject.

Material and Methods: For this purpose, geriatric patients with basic education and below, undergoing non-cardiac surgery and general anesthesia were administered the mini-mental state test three times: preoperatively, 2, and 24 hours after the termination of anesthesia.

The correlation between the cognitive functions of the patients measured with the sub-item and total mean scores of MMST and time of measurement, their age, gender, educational background, and ASA scores were evaluated.

Results: In all cases, for all the scores obtained in MMST, there was a significant decrease in the scores measured at the second postoperative hour compared to the preoperative ones. While the scores measured at the 24th postoperative hour showed an increase, decreasing the difference with the preoperative scores of the patients, they still failed to reach their preoperative level. These changes between measurements are not always statistically significant. Compared to the preoperative period, the decrease in the mean attention and calculation score at the second postoperative hour was higher in females than in males, and the increase in the mean attention and calculation score at the 24th postoperative hour in comparison with the second postoperative hour was higher in females than in males ($p<0.05$).

Discussion: In order for the subject to be clear and become classical knowledge, studies on a wider sample are necessary. This would be beneficial in terms of general anesthesia practices in geriatric patients.

Keywords

Anesthesia; Geriatric patients; Cognitive functions

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Introduction

It has long been emphasized that general anesthesia practices affect cognitive functions negatively. In many studies, it has been shown that impairment in psychomotor and cognitive functions persists for 10-12 hours after exposure to anesthetic agents, and this deterioration can last for 1-2 days with sensitive tests [1].

There are studies showing that advanced age, in particular, is one of the main risk factors for the development of postoperative cognitive dysfunction [2,3,4,5].

Postoperative cognitive dysfunction is defined as a decline in cognition and memory [2, 3]. Postoperative cognitive impairment covers a wide range of problems from postoperative cognitive dysfunction (impaired cognition) to dementia (memory impairment) and postoperative delirium (loss of consciousness). Although mental functions typically decrease to the lowest levels in the early postoperative period, the majority of patients return to preoperative levels in the first postoperative week [2]. In contrast, elderly patients with preexisting cognitive dysfunction and concomitant medical-based diseases (Diabetes mellitus, hypertension and so on), having undergone certain types of surgery (cardiac operations) are at a high risk for developing postoperative cognitive impairment, and prolonged cognitive deterioration may occur in such patients [2, 4].

Postoperative cognitive impairment occurs more frequently than thought, especially in high-risk patients, such as the elderly [6].

The original aim of the thesis is to examine the effect of the ASA score and personal characteristics (age, gender, and educational background) on the postoperative cognitive functions of the geriatric patients undergoing non-cardiac elective surgery and general anesthesia, through the administration of the Mini-Mental State Test three times (pre-anesthesia, 2, and 24 hours after the termination of anesthesia), and to make recommendations based on the results obtained.

Material and Methods

Upon a review of the fundamental literature at the preparation stage for the study, the standardized mini-mental state test administered to patients with eight years of education or less was chosen as the survey.

The phases of this study were set up with 83 geriatric patients admitted to Ankara Numune Training and Research Hospital of the Republic of Turkey between January 1, 2011 and May 1, 2011, undergoing general anesthesia administered for planned non-cardiac elective general surgery operations (herniorrhaphy, cholecystectomy, mastectomy and so on). Ethics committee approval and patients' informed consent were obtained. From the non-cardiac patients assessed between the specified dates, those meeting the following criteria were included in the study: being 65 and over, having received eight years of education or less, having a mini-mental state test score higher than 17, not having been diagnosed with psychiatric and neurological diseases, not having communication problems (in hearing, seeing, speaking and so on), not having a problem holding a pen, having ASA score II, III, IV (patient groups with ASA scores I and V were excluded due to the low size of the patient population in the former as a result of the high incidence of co-morbid diseases in the geriatric patient group, and the low number of patients undergoing elective surgery in the latter).

We used the Mini-Mental State Test (MMST) for evaluation. MMST was developed by Folstein in 1982, it was first translated into Turkish and standardized by Gungen et al. in 2002 [7]. New regulations for uneducated patients were adapted to Turkish by Keskinoglu et al. in 2008 in Turkey [8]. It is a quantitative and practical test to assess the cognitive states of patients. It consists of 11 questions measuring cognitive functions including temporal and spatial orientation, memory and recall, attention and calculation, orientation, language, and visual structuring. The maximum score is 30 and the minimum score is 0. Scores of 23 and below are indicative of cognitive decline.

Eighty-three patients were examined by the researcher. After a preliminary evaluation, five patients were found not to meet the selection criteria and were excluded from the study. Seventy-eight patients who met the selection criteria were included.

Patients who met the criteria in the first general examination were administered the first MMST, 10 patients among these were excluded from the study because their MMST score was less than 17. The operations of 4 patients with an MMST score above 17 were canceled for various reasons by the relevant clinic planning the operation. While the second MMST was being administered postoperatively, four patients were excluded due to lack of communication for various reasons (pain, agitation and so on). As a result, the number of patients who were administered MMST three times was 60.

Standard monitorization (ECG, noninvasive blood pressure, oxygen saturation) was applied to all patients included in the study. For anesthesia induction, 2-3 mg/kg propofol and 1 μgr/kg fentanyl were used. Before the injection of propofol, 40-60 mg lidocaine was administered as an analgesic for injection pain. In patients who required muscle relaxation and intubation, vecuronium bromide at a dose of 0.08 - 0.1 mg/kg was used. For anesthesia maintenance, 50% N_2O (nitrous oxide) and 50% O_2 and, as inhalation agent, sevoflurane gas were administered.

Statistical Analysis

The patient questionnaire forms were carefully reviewed and the data were converted to numerical values and entered into the SPSS for Windows 11.5 package program. Descriptive statistics were expressed as mean ± standard deviation or median (minimum-maximum) for discrete numerical variables, and as number of cases and (%) for classifiable variables. The sub-item and total mean scores of the Mini-Mental State Test were evaluated by means of "Repeated Measures Analysis of Variance". The "Greenhouse - Geisser Test" was used for comparisons between follow-up times. If the test statistics were found to be significant, "Bonferroni Multiple Comparison Correction Test" was used to identify the situations that caused the significant difference. Statistically significant effects of factors such as age, gender, and ASA score on the mean changes in the sub-item and total scores according to the follow-up times were assessed using the "Greenhouse-Geisser Test Statistics" and significance of the interaction effect was checked. When the interaction effect was found to be significant, the "Student's Test" was used to examine the effect of gender on the changes in orientation score and attention and calculation score.

In addition, with the “Spearman’s Correlation Test”, it was investigated whether the change in the sub-item and total scores of the Mini-Mental State Test is correlated with the educational background. The Wilcoxon Sign Test was used to determine whether the total scores of the Mini-Mental State Test showed a significant change between follow-up times in terms of the degree of impairment. Results for a p-value of <0.05 were accepted as statistically significant.

Power (Power) analysis was done with G * Power 3.1.9.4 statistical software; n = 60, Number of groups = 3, Number of measurements = 3, α = 0.05, Effect Size f = 0.4; Power (1-β) = 0.92.

Results

The demographic characteristics of the cases according to ASA were shown in Table 1.

MMST sub-item and Total Scores for ASA, gender, and age were summarized in Table 2.

Differences in Mean MMST Sub-Item and Total Scores and Educational Background

To eliminate the bias education would form, all the cases in the study were selected from an uneducated group (those having received compulsory education and below). The classification of the cases according to educational background was as follows: 25 (41%) of the cases never attended school, 12 (20%) of them were primary school dropouts, 16 (27%) were primary school graduates, 3 (5%) were secondary school dropouts and 4 (7%) were secondary school graduates. The differences among the cases in terms of educational levels indicated that all the MMST scores of the cases, in general, showed an increase parallel to educational status. Distribution of MMST sub-item and total scores according to the time of measurement and educational background showed that all the mean MMST scores of the cases had a decrease at the second postoperative hour, then had a slight increase at the 24th postoperative hour, but were still lower than those in the preoperative period. When these differences brought about by the time of measurement and educational background were tested with the Greenhouse-Geisser test, it was revealed that the differences in all MMST sub-items (orientation, registration memory, attention and calculation, recall, language) and total scores were not statistically significant (p>0.05). In cases with few years of education, there is a higher decrease in the score at the 24th postoperative hour compared to the preoperative period. This result is statistically significant (r=0.297, p=0.021). Likewise, a decrease in MMST total score at the second postoperative hour compared to the preoperative period is directly proportional to the educational level. This correlation between MMST total score and educational level is statistically significant (r=0.295, p=0.022). The correlations between the other MMST sub-item scores (orientation, registration memory, recall, language) of the cases and the times of measurement and educational background were not statistically significant (p>0.05).

MMST Sub-Item and Total Scores and Monitoring Time

The mean values of the sub-item and total scores of the included cases in the preoperative period and at second and 24th postoperative hours are when the mean values of the MMST sub-item and total scores at different follow-up times or in different measurements (preoperative and second and 24th postoperative hours) were analyzed with the Greenhouse - Geisser test for Repeated Measures Analysis of Variance (Table 3). There is a highly statistically significant difference between the values in the first, second, and third measurements of the MMST sub-item scales (orientation, registration memory, attention and calculation, language), except for recall. When the change in the mean scores obtained by measurements (preoperative, second postoperative hour, 24th postoperative hour) is examined, generally, there was a noticeable decrease in second postoperative hour scores compared to the preoperative period and this gap was either decreased or closed at the 24th postoperative hour. In other words, while the loss of cognitive functions was higher in the patients immediately after recovery from anesthesia, it was observed that these values generally decreased after 24 hours, becoming close to normal, and losses at the second operative hour were not permanent. The p-values reached through the assessment with Bonferroni Multiple Comparison Correction Test of the changes of the Mini-Mental State Test sub-item and total scores obtained in the measurements in terms of follow-up times. (The change in the mean scores obtained by measurements of the recall sub-item was found insignificant, and thus not taken into consideration). All the mean scores obtained at the second postoperative hour were significantly lower than those obtained in the preoperative period. This decrease is highly significant in terms of the total score. When the mean scores obtained at the 24th postoperative hour were compared with those obtained in the preoperative period, there was no significant difference between the preoperative mean scores and 24th postoperative hour mean scores in the orientation, registration memory, attention and calculation sub-items. In other words, the loss in the cognitive functions of cases in terms of registration memory, attention and calculation sub-items measured at the second hour following general anesthesia was completely recovered in the 24th hour measurement. In the comparison of the language sub-item and total mean scores at the 24th postoperative hour and in the preoperative period, the mean scores obtained at the former were significantly lower than the latter. In other words, the cognitive impairment of the patient in these two scales has not disappeared yet. When the mean scores obtained at the postoperative second hour and those obtained at the postoperative 24th hour were compared, the former were generally found to be higher than the latter. However, among these, only the increase in the registration memory and the total score is statistically significant. In other words, when the cognitive functions of the patients at the second hour following general anesthesia were compared with those at the 24th hour, a significant improvement was observed in the registration memory and total scores.

Discussion

The aim of this study was to evaluate with the Mini-Mental State Test the relationship between ASA score, age, gender, and educational background and postoperative cognitive functions in geriatric patients undergoing elective non-cardiac surgery. In order to test our hypothesis and investigate related factors,

Table 1. Demographic Distribution of Cases According to ASA Groups

	ASA II (n=20)	ASA III (n=20)	ASA IV (n=20)	Total (n=60)
Age				
65-69	45% (n=9)	50% (n=10)	15% (n=3)	37% (n=22)
70-74	15% (n=3)	15% (n=3)	45% (n=9)	25% (n=15)
75-79	30% (n=6)	30% (n=6)	25% (n=5)	28% (n=17)
80 +	10% (n=2)	5% (n=1)	15% (n=3)	10% (n=6)
Gender				
Female	45% (n=9)	40% (n=8)	35% (n=7)	40% (n=24)
Male	55% (n=11)	60% (n=12)	65% (n=13)	60% (n=36)
Educational Background				
Never been to school	65% (n=13)	35% (n=7)	25% (n=5)	41% (n=25)
Dropped out of primary school	10% (n=2)	10% (n=2)	40% (n=8)	20% (n=12)
Primary school graduate	20% (n=4)	30% (n=6)	30% (n=6)	27% (n=16)
Dropped out of secondary school	0% (n=0)	15% (n=3)	0% (n=0)	5% (n=3)
Secondary school graduate	5% (n=1)	10% (n=2)	5% (n=1)	7% (n=4)

three different measurements (in the preoperative period and at the second and 24th postoperative hours) were performed, which were used to analyze whether there was any difference between the scores of the six scales of the mini-mental test (orientation, registration memory, attention and calculation, recall, language sub-items, and total score) at different measurement times and whether the individual characteristics of the patients (age, gender, educational status) and ASA scores had any effect on this.

In the selection of the study population, ASA I patients were excluded due to their low number as a result of the high incidence of comorbidities in the geriatric patient group. In addition, ASA V patients were also excluded owing to the low number of such patients undergoing elective surgery.

While planning the study, it was foreseen that, especially in geriatric patients, postoperative cognitive functions would deteriorate more as ASA score increased, requiring sensitive care for these patients during anesthesia and postoperative period, with closer follow-up in clinics. According to our extensive literature review, the relationship between ASA score and postoperative cognitive function deterioration was first investigated in our study, which makes it original.

Postoperative cognitive function impairment has become one of the most important problems of the perioperative period in recent years due to the increasing population of elderly patients [5, 6, 9]. While there were almost no studies on this subject until 50 years ago, they have increased gradually in the last decade, especially after the multicenter studies of Rasmussen et al. [6, 10,11]. However, in almost none of these studies, postoperative cognitive function impairment has been fully or clearly defined; “more importantly”, independent variables that play a role in the etiology and pathogenesis of this problem cannot be identified, either. In determining postoperative cognitive impairment, another crucial problem is that it is yet to be determined which neuropsychological tests should be used for the evaluation of cognitive functions, and the extent to which they are efficient and specific [8].

Table 2. MMST Sub-Item and Total Scores

			Preoperative	Second Post-operative Hour	24th Post-operative Hour	P[a]
ASA Score	Orientation Score	ASA II	8.80 ± 1.20	8.60 ± 1.64	8.70 ± 1.22	0.405
		ASA III	8.85 ± 1.46	8.50 ± 1.79	8.75 ± 1.65	0.173
		ASA IV	8.60 ± 1.50	8.30 ± 1.22	8.35 ± 1.73	0.251
	Registration Memory Score	ASA II	2.75 ± 0.44	2.90 ± 0.31	2.70 ± 0.47	0.050
		ASA III	2.75 ± 0.44	2.90 ± 0.31	2.70 ± 0.47	0.050
		ASA IV	2.90 ± 0.31	2.95 ± 0.22	2.80 ± 0.41	0.251
	Attention and Calculation Score	ASA II	4.20 ± 1.24	3.75 ± 1.86	4.10 ± 1.25	0.113
		ASA III	3.90 ± 1.74	3.65 ± 1.57	3.85 ± 1.73	0.347
		ASA IV	4.00 ± 1.24	3.65 ± 1.60	4.00 ± 1.21	0.081
	Recall Score	ASA II	2.05 ± 0.89	1.85 ± 0.88	2.05 ± 0.89	0.214
		ASA III	1.65 ± 1.18	1.60 ± 0.75	1.70 ± 1.22	0.738
		ASA IV	1.95 ± 0.89	1.70 ± 0.86	1.90 ± 0.85	0.170
	Language Score	ASA II	6.75 ± 1.33	6.65 ± 1.31	6.65 ± 1.31	0.576
		ASA III	7.30 ± 1.17	7.05 ± 1.28	7.05 ± 1.12	0.195
		ASA IV	7.45 ± 1.05	7.00 ± 1.17	7.15 ± 1.23	0.076
	Total MMST Score	ASA II	24.55 ± 3.85	23.75 ± 4.03	24.20 ± 4.12	0.008
		ASA III	24.45 ± 3.78	23.70 ± 3.65	24.05 ± 3.67	0.113
		ASA IV	25.10 ± 3.96	23.60 ± 3.72	24.20 ± 3.93	0.001
Age	Orientation Score	≤ 70	8.63 ± 1.38	8.30 ± 1.78	8.50 ± 1.53	0.121
		> 70	8.87 ± 1.38	8.63 ± 1.27	8.70 ± 1.56	0.217
	Registration Memory Score	≤ 70	2.77 ± 0.73	2.90 ± 0.31	2.70 ± 0.47	0.012
		> 70	2.83 ± 0.38	2.93 ± 0.25	2.77 ± 0.43	0.078
	Attention and Calculation Score	≤ 70	3.83 ± 1.66	3.40 ± 1.89	3.70 ± 1.64	0.108
		> 70	4.37 ± 1.07	3.97 ± 1.35	4.27 ± 1.05	0.083
	Recall Score	≤ 70	1.77 ± 1.01	1.73 ± 0.78	1.80 ± 1.03	0.724
		> 70	2.00 ± 0.98	1.70 ± 0.88	1.97 ± 0.96	0.071
	Language Score	≤ 70	7.10 ± 1.32	6.93 ± 1.41	6.93 ± 1.39	0.174
		> 70	7.23 ± 1.10	6.87 ± 1.07	6.97 ± 1.13	0.063
	Total MMST Score	≤ 70	24.10 ± 3.91	23.27 ± 4.49	23.63 ± 4.21	0.000
		> 70	25.30 ± 2.53	24.10 ± 3.00	24.67 ± 2.70	0.001
Gender	Orientation Score	Male	9.14 ± 1.29	8.92 ± 1.38	9.00 ± 1.47	0.303
		Female	8.17 ± 1.31	7.79 ± 1.56	8.00 ± 1.44	0.025
	Registration Memory Score	Male	2.86 ± 0.35	2.92 ± 0.28	2.78 ± 0.42	0.079
		Female	2.71 ± 0.46	2.92 ± 0.28	2.67 ± 0.48	0.011
	Attention and Calculation Score	Male	4.31 ± 1.19	4.19 ± 1.19	4.19 ± 1.19	0.504
		Female	3.79 ± 1.67	2.92 ± 1.95	3.67 ± 1.63	0.002
	Recall Score	Male	1.94 ± 1.01	1.61 ± 0.84	1.91 ± 1.01	0.069
		Female	1.79 ± 0.98	1.88 ± 0.80	1.79 ± 0.97	0.604
	Language Score	Male	7.47 ± 1.16	7.08 ± 1.16	7.28 ± 1.16	0.016
		Female	6.71 ± 1.16	6.63 ± 1.35	6.46 ± 1.25	0.156
	Total MMST Score	Male	25.72 ± 2.54	24.72 ± 3.18	25.19 ± 2.73	0.001
		Female	23.17 ± 3.77	22.13 ± 4.20	22.58 ± 4.07	0.002

[a]: Repeated Measures Analysis of Variance

Table 3. Distribution of MMST Sub-item and Total Scores According to Follow-Up Times

	Preoperative	24th Postoperative 2nd Hour	24th Postoperative Hour	P[a]
Orientation	8.75 ± 1.37	8.47 ± 1.55	8.60 ± 1.53	0.009
Registration Memory	2.80 ± 0.40	2.92 ± 0.28	2.73 ± 0.45	0.003
Attention and Calculation	4.10 ± 1.41	3.68 ± 1.65	3.98 ± 1.40	0.002
Recall	1.88 ± 0.99	1.72 ± 0.83	1.88 ± 0.99	0.305
Language	7.17 ± 1.21	6.90 ± 1.24	6.95 ± 1.25	0.002
Total	24.70 ± 3.31	23.68 ± 3.81	24.15 ± 3.55	0.001

a: Repeated Measures Analysis of Variance, Greenhouse - Geisser test, MMST is a test that provides an assessment of cognitive impairment by asking patients various questions. The highest score is 30 and a score of 23 or less indicates cognitive impairment. It has high validity and reliability, and it is short and easy to apply [12]. The same test was translated into Turkish for both educated and untrained patients and tested and validated for reliability [7, 8].

Neurologists have long been aware that cognitive functions show a gradual decline with advancing age. In the study conducted by Zhang et al., the prevalence of dementia in individuals 65 years and older was found to be 4.6% [13]. In a similar study, Paraïso et al. found this rate to be 3.7% [14]. In a review by Fagundes et al. in 2011, the incidence of dementia in patients over 65 years of age ranged between 5.1 and 19% [15]. The impact of anesthesia has further complicated the fact that there is a decline in cognitive functions with increasing age, urging researchers to conduct studies on this subject. For the patients included in our study, according to the cut-off point of 70 years of age, there was no statistically significant difference between the age ranges in terms of mean MMST sub-item and total scores obtained in the preoperative period and at the second and 24th postoperative hours. In other words, in the studied geriatric patients undergoing anesthesia, the impact of age differences among the patients on MMST scores was not at a significant level. However, various researchers have shown that age affects MMST scores, and increasing age leads to a decrease in scores both within groups of geriatric patients and in comparisons between young and geriatric patient groups, which is statistically significant. In an international study conducted in 1998 on postoperative cognitive functions, of the 1218 patients undergoing non-cardiac major surgery at the age of 60 and over, 26% was found to have cognitive function impairment one week after surgery while deterioration persisted in 10% of them three months after surgery [6]. The incidence of postoperative cognitive function impairment in geriatric patients undergoing orthopedic surgical intervention has been reported to be between 44% – 61% [16]. In the study by Zhang et al., gender (female), like age, was defined as an independent risk factor for dementia [13]. In the cases included in our study, the decrease in the attention and calculation score at the second postoperative hour compared to the preoperative period was statistically more significant in females than in males. Parallel to this, there was a higher increase in the attention and calculation score of females at the 24th postoperative hour compared to the second postoperative hour. Namely, the attention and calculation scores of female patients included in the study improved more slowly after general anesthesia. The study by Di Carlo et al. showed that postoperative cognitive functions are affected more negatively in females [17]. In our study, though, no statistically significant correlation was found between gender and total MMST scores. Similar to our study, many other studies have shown no relationship between gender and differences in postoperative cognitive functions [18]. Studies have demonstrated that individuals with lower education levels experience impairment in cognitive functions earlier, with an increased incidence of dementia in their group [19,20]. Moreover, although higher levels of education are shown to be protective against dementia, no exact reason for this has been suggested yet [21]. Educational background is considered a preoperative risk factor for postoperative cognitive function impairment [22]. Cognitive functions at postoperative periods show a higher decline in individuals with low education levels and advanced age [22]. In the study by Ho et al., educational level was presented as a factor in postoperative cognitive function impairment [23].

Conclussion

Whereas ASA scores differed significantly in terms of MMST sub-item and total scores at the first, second, and third measurements in ASA II and ASA IV groups ($p<0.05$), the difference in ASA III group was statistically insignificant ($p>0.05$).

For the patients included in our study, according to the cut-off point of 70 years of age, there was no statistically significant difference between the age ranges in terms of mean MMST sub-item and total scores obtained in the preoperative period and at the second and 24th postoperative hours ($p>0.05$). In other words, in the studied geriatric patients undergoing anesthesia, the impact of age differences among the patients on MMST scores was not at a significant level.

In the cases included in our study, the decrease in the attention and calculation score at the second postoperative hour compared to the preoperative period was statistically more significant in females than in males. Parallel to this, there was a higher increase in the attention and calculation score of females at the 24th postoperative hour compared to the second postoperative hour ($p<0.05$).

The decrease in the attention and calculation score at the 24th postoperative hour compared to the preoperative period was directly proportional to educational background. The decrease in the total score at the second postoperative hour compared to the preoperative period was also directly proportional to the educational background ($p<0.05$).

The orientation scores of the patients had a significant decrease at the second postoperative hour compared to the preoperative period ($p=0.036$). In the registration memory score, there was a significant increase at the second postoperative hour compared to the preoperative period, but a significant decrease at the 24th postoperative hour compared to the second postoperative hour ($p<0.05$). The attention and calculation score was found to have a significant decrease at the second postoperative hour compared to the preoperative period ($p=0.011$). There is no significant difference between the recall scores of patients at different measurement times ($p>0.05$). In language scores, there was a significant decrease at both second and 24th postoperative hours compared to the preoperative period ($p<0.05$). As for the total MMST score, there was a significant decrease at the second postoperative hour compared to the preoperative period, but a significant increase at the 24th postoperative hour compared to the second postoperative hour ($p<0.05$). However, the total score at the 24th postoperative hour was significantly lower compared to the preoperative period ($p<0.001$). The analysis of the impacts of anesthesia on cognitive functions is crucial. Further analyses should be carried out on a larger patient series.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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